Remarks

Claims 1, 12, 14-18, 27, 41-44, and 54-63 were pending in the application. Claims 1 and 27 are amended herein. Claims 12 and 56-63 are canceled herein without prejudice. No new matter is added. Therefore, after entry of this Amendment, **claims 1, 14-18, 27, 41-44, 54, and 55** are pending in this application. Consideration of the pending claims is requested.

Claim Rejections – U.S.C. § 102

Claims 27 and 54 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by O'Donnell *et al., Am. J. Path.* 154:1171-1180, 1999). Applicants request reconsideration in light of the amendments herein.

The Office asserts that O'Donnell *et al.* identify "TNF-α as a compound that inhibits the viability of HUVECs, an angiogenesis phenotype in the cell based assay, and inherently, identifies a compound that inhibits angiogenesis" (Office action, page 3, first paragraph). However, the Office is ignoring a portion of claim 27 to conclude that the teachings of O'Donnell *et al.* anticipate this claim. Claim 27 recites "performing a cell-based assay, *which assay produces an angiogenesis phenotype* in said endothelial cell *in the absence of the compound*..." O'Donnell *et al.* do not disclose a cell-based assay that produces any angiogenesis phenotype in the absence of the compound (TNFα). Rather, TNFα produces a phenotype (apoptosis), which is inhibited by Gas6 (see, *e.g.,* Figure 8). This is essentially no different than the Healy *et al.* reference (*Am. J. Physiol. Lung Cell Mol. Physiol.* 280:L1273-L1281, 2001) cited in previous Office actions (*e.g.,* Office action dated June 23, 2008), which disclosed that Gas 6 decreased apoptosis induced by serum-free medium (see, *e.g.,* Healy *et al.*, Figures 8 and 10). The only difference is that in O'Donnell *et al.,* apoptosis is induced by TNFα, rather than serum-free medium.

As described in O'Donnell *et al.*, in the absence of the compound (TNFα), the cells have no "angiogenesis phenotype" as recited in claim 27; they are merely cells in culture. As such, TNFα does not inhibit an angiogenesis phenotype. Thus, O'Donnell *et al.* do not disclose a cell-based assay which produces an angiogenesis phenotype in the absence of a test compound, nor

do they disclose identifying a compound that inhibits an angiogenesis phenotype, and the reference does not anticipate claims 27 and 54.

Despite Applicants' assertion that claim 27 is not anticipated by O'Donnell *et al.,* solely in order to expedite prosecution, claim 27 is amended to recite "performing a cell-based assay, which assay produces an angiogenesis phenotype selected from the group consisting of αvβ3 expression, tube formation, and haptotaxis..." Support for this amendment is found throughout the specification, for example at page 30, lines 19-29; page 32, lines 25-30; and original claim 12. Claims 12 and 63 are canceled herein in light of the amendment to claim 27. O'Donnell *et al.* do not disclose a cell-based assay including αvβ3 expression, tube formation or haptotaxis. Therefore, O'Donnell *et al.* does not anticipate claim 27 or dependent claim 54 and withdrawal of this rejection under 35 U.S.C. § 102(b) is respectfully requested.

Claims 1, 14, 15, 16, 18, 27, 41, 42, 44, 54-58, 60, and 61 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Mor (U.S. 2003/0157573). Claims 56-58, 60, and 61 are canceled herein. Applicants request reconsideration of claims 1, 14-16, 18, 27, 41, 42, 44, 54, and 55 in light of the amendments herein.

The Office asserts that Mor discloses identifying an Axl inhibitor by determining the ability of compounds to inhibit Axl kinase activity in cells, determining inhibition of Axl kinase activity *in vitro*, and by determining cell survival, differentiation, or proliferation response to the compound (Office action, page 4, second paragraph). Claim 1 is amended to recite "performing a cell-based assay, which assay produces an angiogenesis phenotype selected from the group consisting of αvβ3 expression, tube formation, and haptotaxis..." Support for this amendment is found throughout the specification, for example at page 30, lines 19-29; page 32, lines 25-30; and original claim 12. Claim 62 is canceled herein in light of the amendment to claim 1. Claim 27 is similarly amended, as discussed above. Mor does not disclose a cell-based assay including αvβ3 expression, tube formation or haptotaxis. Therefore, Mor does not anticipate independent claims 1 or 27 or dependent claims 14-16, 18, 41, 42, 44, 54, and 55, and withdrawal of this rejection under 35 U.S.C. § 102(e) is respectfully requested.

Claim Rejections – U.S.C. § 103

Claims 12, 17, 43, 59, 62, and 63 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Mor, further in view of Klinghoffer *et al.* (U.S. 2004/0077574), further in view of O'Donnell *et al.*, further in view of Varner and Cheresh (*Curr. Opin. Cell Biol.* 8:724-730, 1996). Claims 12, 59, 62, and 63 are canceled herein. Applicants request reconsideration of the pending claims to the extent the rejection is maintained in view of the amendments herein.

As an initial matter, Applicants note that claim 17 depends from claim 1 and claim 43 depends from claim 27. Independent claims 1 and 27 have not been rejected under 35 U.S.C. § 103(a). If an independent claim is nonobvious, then any claim depending from the independent claim is nonobvious (MPEP § 2143.03, citing *In re Fine* 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)). Therefore, claims 17 and 43 cannot be obvious, unless claims 1 and 27 are rejected as obvious. In spite of this, and in light of the amendments to claims 1 and 27 above, the obviousness rejection as applied to canceled independent claims 62 and 63 is addressed below.

The Office acknowledges that Mor does not disclose use of RNAi or assaying $\alpha v\beta 3$ expression, tube formation, or haptotaxis (Office action, page 5, third paragraph). The Office asserts that it would have been obvious to combine Mor with Klinghoffer *et al.* to utilize RNAi molecules in the screening method of Mor (Office action, page 6, third paragraph). The Office also asserts that it would have been obvious to combine Mor, O'Donnell *et al.*, and Varner and Cheresh because O'Donnell *et al.* discloses that Axl may be involved in tube formation during angiogenesis, and Varner and Cheresh disclose a role for $\alpha v\beta 3$ in angiogenesis (Office action, page 6-7).

Claims 1 and 27 are amended as discussed above to recite "an angiogenesis phenotype selected from $\alpha v\beta 3$ expression, tube formation, and haptotaxis…" The Office has provided no evidence that one of skill in the art would be motivated to combine Mor and Klinghoffer *et al.* to arrive at the claimed methods. Mor does not discuss angiogenesis phenotypes in general, nor $\alpha v\beta 3$ expression, tube formation, or haptotaxis specifically. Mor is focused on identifying compounds of use in treating renal disease, specifically glomerulosclerosis and renal fibrosis in

diabetic nephropathy (*e.g.*, paragraphs [0020], [0022], and [0033]). Klinghoffer *et al.* relates solely to RNAi molecules, and does not cure the deficiencies of Mor.

O'Donnell *et al.* state that Axl is expressed by endothelial cells in capillaries and the homophilic binding between extracellular domains "suggests a role in *cell adhesion* which *could be relevant* to tube formation in angiogenesis. Vascular smooth muscle cell expression has been previously noted in the rat and *may suggest* involvement of Axl in *some other aspect of vascular function*" (O'Donnell *et al.*, page 1176, col. 2, emphasis added). However, the focus of O'Donnell *et al.* is on the effects of Gas6 on apoptosis or cell viability in cells which have been serum-deprived or exposed to TNFα (O'Donnell *et al.*, page 1172, first full paragraph and pages 1174-1176). Statements by O'Donnell *et al.* regarding the potential role of Axl in tube formation are speculative at best, and suggest equally that Axl may have some entirely different function in endothelial cells. The Office has not provided any evidence that one of skill in the art would have considered $\alpha v\beta 3$ expression relevant or useful in the assays disclosed by Mor, nor would this have been predictable.

Based on the foregoing, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103(a).

Conclusion

Applicants respectfully submit that the claims are now in condition for allowance. If any issues remain, the Examiner is requested to contact the undersigned to arrange a telephonic interview prior to the preparation of any further written action.

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 595-5300
Facsimile: (503) 595-5301

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By /Susan W. Graf/
Susan W. Graf, Ph.D.
Registration No. 60,432

cc: Docketing